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The TOPPIC Trial: a randomised, double-blind parallel-group trial of mercaptopurine versus placebo to prevent recurrence of Crohn's disease following surgical resection in 240 patients

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[A: We have edited your paper to avoid repetition, enhance readability, reduce length, and achieve consistency with Lancet style. Please check that all drug names are the rINNs (recommended international non-proprietary names) where possible, and please ensure that the dose, route, and frequency of administration are correct. Please note that we try to keep use of abbreviations to a minimum so I have spelt out where necessary]



Mercaptopurine versus placebo to prevent recurrence of Crohn's disease after surgical resection (TOPPIC): a multicentre, double-blind, randomised controlled trial

Craig Mowat, Ian Arnott, Aiden Cahill, Malcolm Smith, Tariq Ahmad, Sreedhar Subramanian, Simon Travis, John Morris, John Hamlin, Anjan Dhar, Chuka Nwokolo, Cathryn Edwards, Tom Creed, Stuart Bloom, Mohamed Yousif, Linzi Thomas, Simon Campbell, Stephen J Lewis, Shaji Sebastian, Sandip Sen, Simon Lal, Chris Hawkey, Charles Murray, Fraser Cummings, Jason Goh, James O Lindsay, Naila Arebi, Lindsay Potts, Aileen J McKinley, John M Thomson, John A Todd, Mhairi Collie, Malcolm G Dunlop, Ashley Mowat, Daniel R Gaya, Jack Winter, Graham D Naismith, Holly Ennis, Catriona Keerie, Steff Lewis, Robin J Prescott, Nicholas A Kennedy, Jack Satsangi, for the TOPPIC Study Group*

Summary [A: we only include primary and safety data in the Summary and so it has been edited accordingly]

Background Up to 60% of patients with Crohn's disease need intestinal resection within the first 10 years of diagnosis, and postoperative recurrence is common. We investigated whether mercaptopurine can prevent or delay postoperative clinical recurrence of Crohn's disease.

Methods We did a randomised, placebo-controlled, double-blind trial at 29 UK secondary and tertiary hospitals of patients (aged >16 years in Scotland or >18 years in England and Wales) who had a confirmed diagnosis of Crohn's disease and were undergoing [A: or had undergone? (the inclusion criteria in the methods section state that patients had undergone intestinal resection in the previous 3 months)] intestinal resection. Patients were randomly assigned (1:1) by a computer-generated web-based randomisation system to [A: oral?] daily mercaptopurine at a dose of 1 mg/kg body weight rounded to the nearest 25 mg or placebo; patients with low thiopurine methyltransferase activity received half the normal dose. Patients and their carers and physicians were masked to the treatment allocation. Patients were followed up for 3 years. The primary endpoint was a composite of clinical recurrence of Crohn's disease (Crohn's Disease Activity Index >150 plus 100 point increase in score) and the need for anti-inflammatory rescue treatment or primary surgical intervention. Primary and safety analyses were by intention to treat. Subgroup analyses by smoking status, previous thiopurines, previous infliximab or methotrexate, previous surgery, duration of disease, or age at diagnosis were also done. This trial is registered with the International Standard Randomised Controlled Trial Register (ISRCTN89489788) and the European Clinical Trials Database (EudraCT number 2006-005800-15).

Findings Between June 6, 2008, and April 23, 2012, 240 patients with Crohn's disease were randomly assigned: 128 to mercaptopurine and 112 to placebo. All patients received at least one dose of study drug, and no randomly assigned patients were excluded from the analysis. 16 (13%) of patients in the mercaptopurine group versus 26 (23%) patients in the placebo group reached the primary endpoint (adjusted hazard ratio [HR] 0.535 [A: please give to 2 dp], 95% CI 0.27–1.06; $p=0.07$; unadjusted HR 0.53, 95% CI 0.28–0.99; $p=0.046$). In a subgroup analysis, three (10%) of 29 smokers in the mercaptopurine group and 12 (46%) of 26 in the placebo group reached the primary endpoint (HR 0.13, 95% CI 0.04–0.46), compared with 13 (13%) of 99 non-smokers in the mercaptopurine group and 14 (16%) of 86 in the placebo group (0.90, 0.42–1.94; $p_{\text{interaction}}$ [A: correct?]=0.018). None of the other planned subgroup analyses were significant (previous thiopurines, previous infliximab or methotrexate, previous surgery, duration of disease, or age at diagnosis). The incidence and types of adverse events were similar in the mercaptopurine and placebo groups. One patient on placebo died of ischaemic heart disease. Adverse events caused discontinuation of treatment in 39 (30%) of 128 patients in the mercaptopurine group versus 41 (37%) of 112 in the placebo group.

Interpretation [A: this section should be an interpretation of the key results, not a repetition of the main findings. Please provide a sentence or two to explain the importance of these findings (eg, should mercaptopurine be recommended for prevention of post-op recurrence? What future studies are needed?)]

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Introduction

Crohn's disease is a chronic, relapsing inflammatory bowel disease. Estimates of the frequency of surgical resection in Crohn's disease vary. Historical data suggest

that up to 60% of patients need a major abdominal resection within 10 years of diagnosis.¹ [A: ref for 60% correct?] However, more recent population-based data suggest this figure is as low as 29% at 7 years.² [A: ref 1

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PII

*Members listed in appendix
pp 2–3

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Research in context

Evidence before this study

The first randomised controlled trial of thiopurines for prevention of postoperative Crohn's disease was published in 2000 [A: what did it show?]. However, uncertainty remains about their efficacy in this patient group. We searched the Cochrane Central Register of Controlled Trials until May 24, 2016, and PubMed from Jan 1, 1974, to May 24, 2016, with the terms "(azathioprine OR mercaptopurine OR thiopurine) AND Crohn's AND (postoperative OR resection OR hemicolectomy OR ileectomy OR surgical procedures OR surgery) AND trial", with no language restrictions. We identified three previous systematic reviews with meta-analyses comparing thiopurines with either placebo or mesalazine: two published by the Cochrane Collaboration and one by another group. The two Cochrane reviews differed in their choice of timepoint to assess outcome and in their handling of loss to follow-up. The earlier [A: the earlier Cochrane review?] review compared clinical recurrence at a standard time of 12 months across all studies and used the number of clinical relapses. [A: used the number of clinical relapses as what? The measure of clinical recurrence?] Clinical relapse differed significantly between thiopurines and placebo (risk ratio 0.59, 95% CI 0.38–0.92 favouring thiopurines). The more recent Cochrane meta-analysis used the end of study, which varied between 1 year and 2 years, and regarded anyone who did not complete the study as a treatment failure. This study reported a benefit for thiopurines compared with placebo (risk ratio 0.74, 95% CI 0.58–0.94). The Grading of Recommendations Assessment, Development and Evaluation [A: correct expansion of GRADE?] score for the evidence was low. No further published randomised controlled trials were identified that compared thiopurines with placebo since the most recent Cochrane [A: correct?] meta-analysis. [A: what did the third meta-analysis show?]

deleted because I presumed this is the older data] Postoperative recurrence is common within 2 years, in the form of endoscopic signs (72–98% of patients) or clinical symptoms (37–70%), with re-operation rates 40 of endoscopic and clinical recurrence was marked by [A: please clarify—do you mean “the proportion of patients needing surgery increasing by 5% per year” (rather than “with 5% of patients per year needing surgery”)?]

Strategies to prevent or delay postoperative recurrence of 45 Crohn's disease are of major clinical importance. However, there is a paucity of evidence to support any particular drug treatment strategy.^{5,6} Azathioprine and mercaptopurine have an established role in inducing remission, and in the maintenance of medically induced 50 remission, in patients with Crohn's disease. These drugs are recommended in treatment algorithms for patients at high risk of postoperative relapse,⁴ but the evidence to support this, and the evidence that clinical parameters can [A: OK? or “might”?] predict patients at high risk of relapse, 55 is weak. A meta-analysis⁷ showed that efficacy data for thiopurines in this setting were inconclusive and, aside

Added value of this study

TOPPIC is, to our knowledge, the largest randomised controlled study of thiopurines for postoperative prevention of Crohn's disease, and the largest interventional study of any kind for this indication, with 240 patients enrolled. We found no significant difference between mercaptopurine and placebo for the primary endpoint, a composite of clinical recurrence of Crohn's disease (Crohn's Disease Activity Index >150 plus 100 point increase in score) and the need for anti-inflammatory rescue treatment or primary surgical intervention. [A: addition ok? We need to mention the primary outcome here] In a subgroup analysis, smoking was predictive of clinical recurrence within 3 years of surgery ($p_{\text{interaction}}=0.018$), and mercaptopurine was effective at preventing clinical recurrence only in patients who smoked [A: OK?]. [A: edits OK? stating “the most important” implies both that other factors in the subgroup analysis showed significant differences between groups and that the subgroups were compared with one another]

Implications of all the available evidence

From our data, combined with those included in previous Cochrane meta-analyses, we calculated risk ratio of 0.57 (0.38–0.85) in favour of mercaptopurine (appendix p 11). [A: 0.58, 0.41–0.82 according to appendix p 11. Which is correct?] We confirm that smoking affects the clinical course of Crohn's disease, as well as response to treatment, whereas no differences were reported by age, sex, or a history of previous surgery. The risk of recurrence in smokers was the most consistent finding in Buisson and colleagues' review, with an odds ratio of 2.0. Smoking cessation should be a priority in patients with Crohn's disease after surgery.

from smoking, there were no consistent predictors of postoperative relapse. A Cochrane review⁸ also concluded that the evidence supporting thiopurines for the reduction of endoscopic and clinical recurrence was marked by [A: please clarify “evidence...was insufficient because of”?] the small numbers of patients included and flawed study designs. The value of thiopurine metabolites in patients with Crohn's disease is unknown.⁹ [A: is this ref correct? I cannot find mention of thiopurine metabolites in the reference] More recently, [A: than what?] the role of biological treatments in this specialty has received substantial attention. After smaller randomised studies of infliximab,^{9,10} [A: what did these trials show that is relevant to the POCER study?] findings from the POCER study¹¹ showed that targeted escalation of immune-modulatory treatment (ie, thiopurines followed by adalimumab) in patients with early endoscopic evidence of recurrence might [A: OK? or “seems to”?] delay subsequent endoscopic, although not clinical, recurrence.

We therefore aimed to establish whether mercaptopurine, compared with placebo, can prevent or

delay postoperative clinical recurrence of Crohn's disease in patients needing anti-inflammatory rescue treatment or surgery. [A: edited to describe only the primary aim; secondary objectives moved to Outcomes section]

Methods

Study design and patients

TOPPIC was a randomised, placebo-controlled, double-blind study done at 29 secondary and tertiary UK hospitals. The study was approved by the Scotland 'A' Research Ethics Committee. The full protocol is available [online](#).

Patients aged at least [A: correct? (as in your protocol, rather than patients aged older than 16)] 16 years (Scotland) or 18 years (England and Wales) who had a diagnosis of Crohn's disease and an ileo-colic or small bowel resection within the preceding 3 months were eligible for inclusion.¹² [A: please clarify why ref ¹² is relevant to this sentence. Did you use Lennard-Jones' definition of Crohn's disease?] Key exclusion criteria were [A: correct that these are just the key exclusion criteria and others are listed in the appendix?] residual active Crohn's disease present after surgery, known intolerance or hypersensitivity to thiopurines, known need for further surgery, strictureplasty alone, formation of a stoma, active or untreated malignancy, absent thiopurine methyltransferase activity, substantial abnormalities of liver function tests or full blood count, and pregnancy. The [appendix](#) (p 4) lists all inclusion and exclusion criteria. Before randomisation, postoperative infections were treated and existing treatments for Crohn's disease stopped [A: was there any wash-out period for existing treatments or was mercaptopurine begun immediately?]. The protocol was amended [A: please specify exact date] to include patients successfully treated for a malignancy and in remission for at least 5 years and to exclude those receiving treatment for active Crohn's disease at random allocation. All patients provided written informed consent. [A: when? Before enrolment?]

Randomisation and masking

Patients were randomly assigned (1:1) to mercaptopurine or placebo using a computer-generated web-based randomisation system managed by the Edinburgh Clinical Trials Unit (University of Edinburgh, Edinburgh, UK) and stratified according to smoking status at baseline and recruiting site (block sizes of two or four). Patients' details were entered into the randomisation system before random allocation and were concealed at randomisation. Patients and their carers and physicians were masked to the treatment allocation. Blood monitoring results were reviewed by an independent central clinician [A: one of the authors? If so, please provide initials] masked to treatment allocation and to mean corpuscular volume results. [A: How was masking achieved? (Eg, use of tablets identical in appearance)]

The appendix (p 5) details the dose reduction algorithm. To protect masking, investigators were informed that sham dose reductions were planned for patients on placebo. However, on the advice of the data monitoring committee, sham dose reductions did not occur; the investigators were not informed of this.

Procedures

Patients received once daily mercaptopurine, at a dose of 1 mg/kg body weight rounded to the nearest 25 mg, or placebo [A: orally?]. Patients with low thiopurine methyltransferase activity were prescribed half the normal dose.

Baseline assessments included [A: or "were"? ie, is this a complete list of prespecified baseline assessments?] Crohn's Disease Activity Index (CDAI); patient-reported outcome measures, including the Inflammatory Bowel Disease Questionnaire (IBDQ); a physical examination; and a blood sample for 6-thioguanine nucleotide concentrations (6-thioguanine and 6-methylmercaptopurine). We also took additional blood samples for genetic and serological analysis and will report those results separately. Treatment was planned for 3 years, with dose adjusted for changes in bodyweight. The appendix (p 6) describes which procedures were done at which timepoints. Blood monitoring was done weekly for the first 6 weeks and thereafter at 6-weekly intervals. Patients with abnormal results had a dose reduction, temporary cessation, or cessation as per a study algorithm (appendix p 4). Patients with acute [A: OK? If not, please clarify "Profound" in this context] nausea or persistent influenza-like symptoms also received a dose reduction, according to the protocol. If abnormal parameters improved after a temporary cessation, treatment was recommenced at a lower dose. At each study visit, the following data were collected: CDAI, physical examination, concomitant medications, and patient-reported outcomes, including the IBDQ (appendix p 6). Samples for assay of faecal calprotectin, 6-thioguanine, and 6-methylmercaptopurine were collected at randomisation and weeks 13, 49, 103, and 157. [A: correct?] Faecal samples were stored on site at -80°C and then shipped on dry ice to a central laboratory (Gastrointestinal Laboratory, Western General Hospital, Edinburgh, UK) for analysis with the CALPRO Calprotectin ELISA test (ALP; NovaTec Immundiagnostica, Frankfurt, Germany). Samples were stored in a freezer until the patient exited the study, and all samples for an individual were then tested [A: OK? If not, please clarify "run"] at the same time. The Edinburgh laboratory has a coefficient of variation of 10% for faecal calprotectin (based on assessments of the entire sample processing pipeline). 6-thioguanine and 6-methylmercaptopurine were analysed by the Viapath Purine Research Laboratory [A: please specify location]; thioguanine nucleotides and methylated mercaptopurine nucleotides were hydrolysed to the base by boiling in

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For the protocol see [XXXXX](#)

See Online for appendix

acid [A: which acid?] and the bases (thioguanine and methylmercaptopurine) measured by ultraviolet absorption with separation on an ultra-performance liquid chromatography [A: correct expansion of UPLC?] system. Colonoscopy was done at 49 and 157 weeks after randomisation.

Outcomes

The composite [A: OK? to distinguish from the secondary endpoint?] primary outcome was clinical recurrence, defined as a CDAI score of over 150 and a 100-point increase from baseline, and the need for anti-inflammatory rescue treatment or primary surgical intervention. Secondary outcomes were clinical recurrence, defined as reaching either of the individual components of the primary outcome (ie, either a CDAI score of >150 and a 100-point increase from baseline, or the need for anti-inflammatory rescue treatment or primary surgical intervention); endoscopic recurrence, defined as a Rutgeerts score of at least i2; Crohn's Disease Endoscopic Index of Severity (CDEIS) score;^{13,14} and quality of life, measured by changes in IBDQ scores. [A: in the statistical analysis section you also mention EQ-5D. Should this be added here? Please clarify] Adverse events were assessed by investigators at [A: OK? If not, by who?] the participating sites in accordance with the trial protocol. [A: using what scale? CTCAE? What version?]

Statistical analysis

A sample size of 234 patients was needed to give 80% power to detect a reduction in the frequency of recurrence from 50% in the placebo group to 30% in the treatment group by 3 years at the 5% level of significance.

Analyses were by intention to treat. For the primary analysis, we used a Cox proportional hazards model with terms for treatment and the variables on which the randomisation was stratified (smoking status and recruitment site), adjusted for baseline values of previous treatment with mercaptopurine and previous treatment with azathioprine. We present adjusted and unadjusted Cox proportional hazard ratios (HRs) for the comparison of mercaptopurine versus placebo (reference), with a HR of less than one suggesting a treatment effect in favour of mercaptopurine. For both primary and secondary outcomes, the adjusted analysis was judged to be the primary analysis. We did predefined subgroup analyses of the primary and secondary outcomes to assess treatment effect in terms of previous medical treatment, previous surgery, smoking status, duration of disease, and age at diagnosis. The interaction between subgroup and treatment was included in the Cox regression model to establish whether the treatment effect differed by subgroup.

We compared endoscopic recurrence between treatment groups using a χ^2 test. CDEIS results at week 157 were compared between treatment groups using a t test [A: what kind of t test? (one or two-sided?)]. The same subgroups were also analysed with respect to endoscopic recurrence and CDEIS scores [A: was this analysis prespecified? Please clarify]. We produced receiver operating characteristic (ROC) curves to calculate the diagnostic accuracy of faecal calprotectin to predict endoscopic recurrence and remission. The optimum cutoff point was calculated by maximising Youden's J statistic. We incorporated faecal calprotectin and 6-thioguanine separately into a Cox proportional hazards model as time-varying covariates. Quality of life, as measured by the IBDQ, was analysed using a change from baseline repeated measures ANCOVA to assess the effect of treatment over time for the overall mean IBDQ score and also the overall total IBDQ score. Quality of life as measured by the EQ-5D system was summarised by treatment group across study visits.

We excluded missing data from any formal statistical analyses, with the exception of statistical analysis of IBDQ data, for which we used several imputation techniques [A: which techniques?]. A data monitoring committee oversaw the trial. Data were analysed in SAS version 9.4.

This trial is registered with the International Standard Randomised Controlled Trial Register (ISRCTN89489788) and the European Clinical Trials Database (EudraCT number 2006-005800-15).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

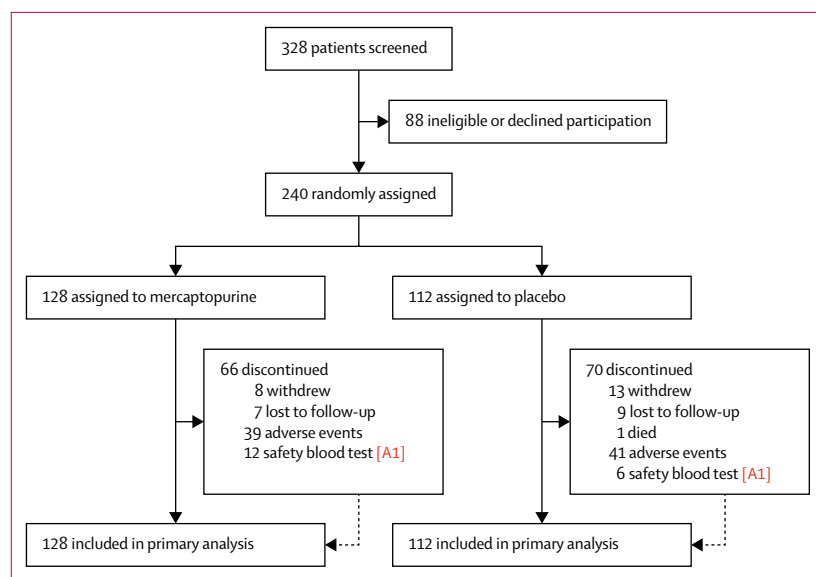


Figure 1: Trial profile

[A: figure redrawn to match standard style. Please check information is correct (we do not include primary or secondary outcome data in the trial profile)] [A1: please clarify your meaning here. What was found on the blood tests that resulted in exclusion?]

	Mercaptopurine (n=128)	Placebo (n=112)
Sex		
Female	79 (62%)	67 (60%)
Male	49 (38%)	45 (40%)
Age (years)		
Mean (SD)	39.2 (12.8)	38.2 (13.4)
Median (IQR)	38 (28–50)	36 (28–48)
Range	17–67	17–75
Age at diagnosis		
≤40 years	103 (80%)	87 (78%)
>40 years	25 (20%)	23 (21%)
Unknown	0	2 (2%)
Present smoker		
Yes*	29 (23%)	26 (23%)
No	99 (77%)	86 (77%)
Duration of Crohn's disease		
≤1 year	37 (29%)	41 (37%)
>1 year	91 (71%)	69 (62%)
Unknown	0	2 (2%)
Duration of Crohn's disease (years)†		
Mean (SD)	7.7 (9.7)	7.6 (9.5)
Median (IQR)	3 (0–11)	4 (0–11)
Range	0–39	0–47
Crohn's disease location‡		
Ileal	54 (42%)	39 (35%)
Colonic	4 (3%)	2 (2%)
Ileocolonic	70 (55%)	70 (63%)

(Table 1 continues in next column)

Results

Between June 6, 2008, and April 23, 2012, 328 patients were screened at 29 centres (appendix p 7), 240 of whom met eligibility criteria, consented to inclusion, and were randomly assigned [A: how many were enrolled?]: 128 to mercaptopurine and 112 to placebo (figure 1). [A: how did 16 more patients end up being assigned to mercaptopurine than placebo, given the 1:1 allocation ratio?] All patients received at least one dose of study drug. 146 (61%) were women and 55 (23%) were smokers (table 1). Baseline characteristics were similar between study groups (table 1). 104 (43%) of 240 patients received study drug at the initial dose [A: added to match statement in Discussion] for the entire 3-year treatment period. The mean treatment period was 22.6 months [A: SD?]: 23.4 months [A: SD?] in the mercaptopurine group versus 21.8 months [A: SD?] in the placebo group. 50 (39%) of 128 patients in the mercaptopurine group and 18 (16%) of 112 in the placebo group had a dose reduction in accordance with the trial protocol. Study drug was discontinued in 66 (52%) of 128 patients in the mercaptopurine groups versus 70 (63%) of 112 in the placebo group for the following reasons: adverse events (59%), blood monitoring results [A: what about these

	Mercaptopurine (n=128)	Placebo (n=112)
(Continued from previous column)		
Previous treatments		
Mercaptopurine‡		
Yes	14 (11%)	5 (4%)
No	114 (89%)	106 (95%)
Azathioprine‡		
Yes	80 (63%)	47 (42%)
No	48 (38%)	64 (57%)
Either thiopurine‡		
Yes	81 (63%)	50 (45%) [A1]
No	47 (37%)	61 (54%) [A1]
Infliximab§		
Yes	21 (16%)	15 (13%)
No	104 (81%)	96 (86%)
Methotrexate‡		
Yes	8 (6%)	7 (6%)
No	120 (94%)	104 (93%)
Other corticosteroids‡		
Yes	97 (76%)	79 (71%)
No	31 (24%)	32 (29%)
Any immunosuppressants‡		
Yes	112 (88%)	86 (77%)
No	16 (13%)	25 (22%)
Previous surgery‡		
Yes	46 (36%)	28 (25%)
No	82 (64%)	83 (74%)

Data are number (%), unless otherwise specified. Some percentages do not add up to 100 because of rounding. *Smoked >1 cigarette per day at study entry. †Data missing for two patients in the placebo group. ‡Data missing for one patient in the placebo group. §Data missing for three patients in the mercaptopurine group and one in the placebo group. [A1: percentage updated based on n/N×100]

Table 1: Demographics and baseline characteristics before randomisation

results led to discontinuation?] (13%), early withdrawal (15%), loss to follow-up (12%), and death (1%). [A: please give numbers in each group for every percentage] The appendix (p 8) summarises data completeness for the study visits. Median follow-up was 36 months (IQR 27.5–36) [A: Please give all data either as whole numbers or to 1 dp] in the mercaptopurine group and 36 months (19.5–36) [A: Please give all data either as whole numbers or to 1 dp] in the placebo group.

The composite primary endpoint of clinical recurrence of Crohn's disease and the need for anti-inflammatory rescue treatment or primary surgical intervention occurred in 42 (18%) of 240 patients: [A: edited to distinguish from secondary clinical recurrence endpoint. OK?] 16 (13%) of 128 in the mercaptopurine group versus 26 (23%) of 112 in the placebo group (adjusted HR 0.535 [A: please give to 2 dp], 95% CI 0.27–1.06; p=0.07; unadjusted HR 0.53, 95% CI 0.28–0.99; p=0.046; figure 2). All 42 patients met the CDAI trigger [A: what do you mean by "met the CADI trigger"?] and had rescue treatment, five (12%) of whom

subsequently went on to have surgery. 15 (27%) of 55 smokers had a clinical recurrence, three (10%) of 29 in the mercaptopurine group and 12 (46%) of 26 in the placebo group (HR 0.13, 95% CI 0.04–0.46), compared with 27 (15%) of 185 non-smokers, 13 (13%) of 99 in the

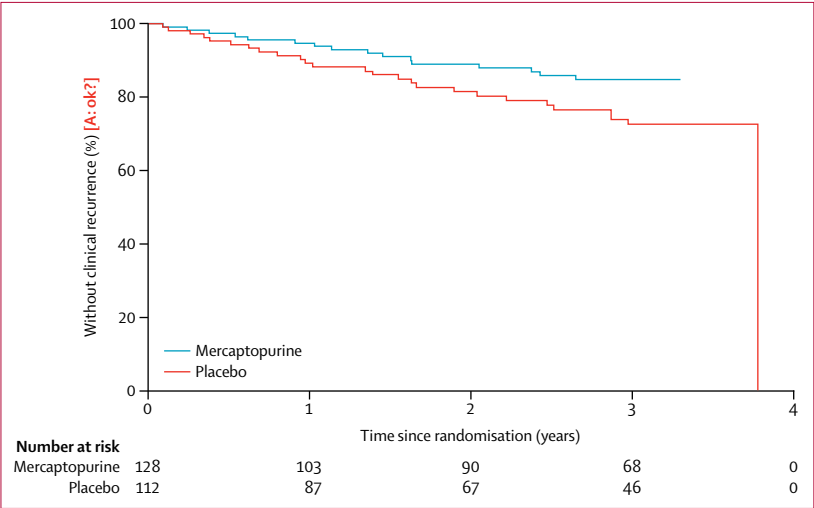


Figure 2: Kaplan-Meier plot of the primary outcome [A: title OK?]
[A: Data for mercaptopurine are shown for longer than placebo. Is this because they show up until the point at which all patients had exited the trial? If so, what is the vertical line for at the end of the mercaptopurine data? Can this be deleted?]

mercaptopurine group and 14 (16%) of 86 in the placebo group (0.90, 0.42–1.94; $p_{\text{interaction}}=0.018$; figure 3). The number needed to treat (NNT) [A: Please add a description of NNT methods to the Methods section and specify whether or not this was a preplanned analysis] was calculated as three for smokers (95% CI 1.7–7.3) [A: is this for benefit or harm? And why do you only give one for smokers but both for non-smokers?] and 31 for non-smokers (95% CI NNT_{benefit} 7.5 to ∞ to NNT_{harm} 14.1) across the entire follow-up period. Previous exposure to treatment, previous surgery, thiopurine status, duration of disease, and age at diagnosis had no effect on the response to study drug (figure 3).

34 (27%) of 128 patients in the mercaptopurine group versus 40 (36%) of 112 in the placebo group experienced the secondary endpoint of clinical recurrence, defined as a CDAI rise or need for rescue treatment or surgery (adjusted HR 0.74, 95% CI 0.44–1.23; $p=0.24$ [A: 0.21 in figure 4. Which is correct?]). In subgroup analyses, mercaptopurine reduced recurrence in smokers only ($p_{\text{interaction}}=0.033$; figure 4).

Of the 208 patients who remained in the study 49 weeks after randomisation, 172 attended for colonoscopy, and a Rutgeerts score was available for 168. [A: please provide numbers in each group] Of these, 121 (72%) had some form of endoscopic recurrence (score >0). [A: please provide numbers in each group] Of the 161 patients who

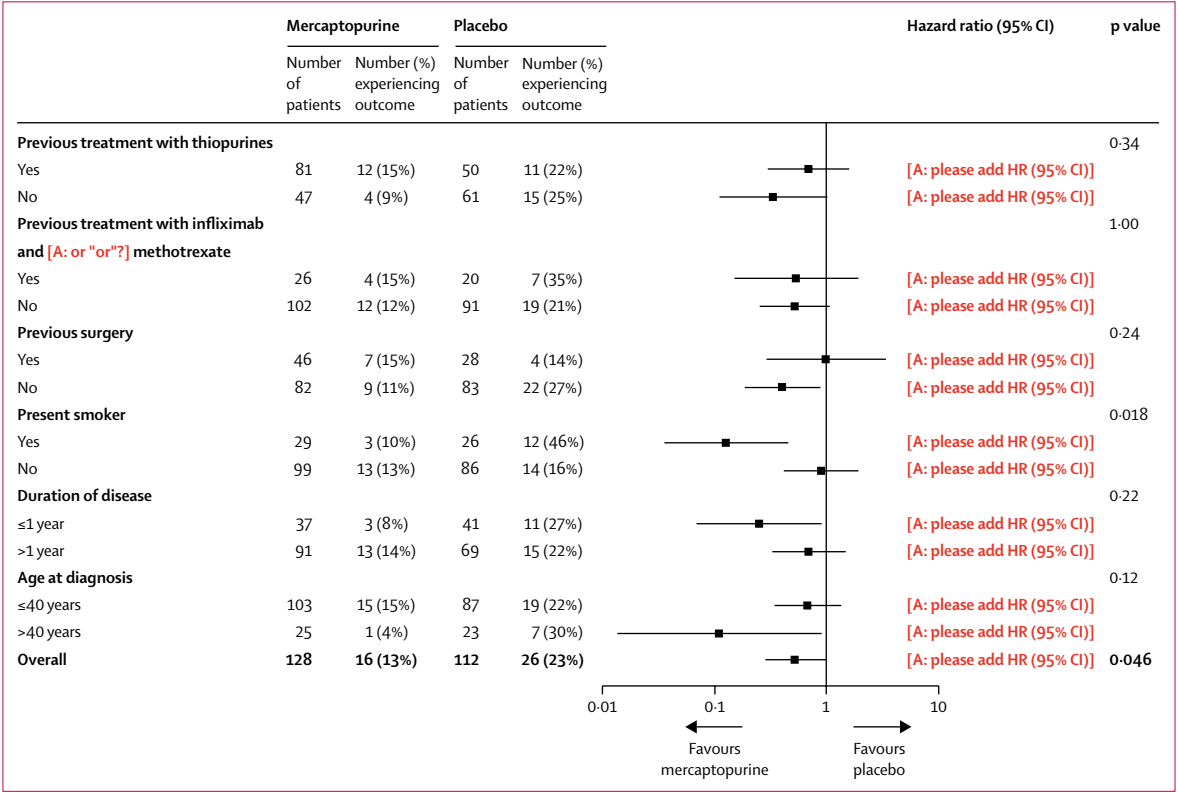


Figure 3: Subgroup analyses of primary outcome [A: title OK?]
[A: are p values $p_{\text{interaction}}$?]

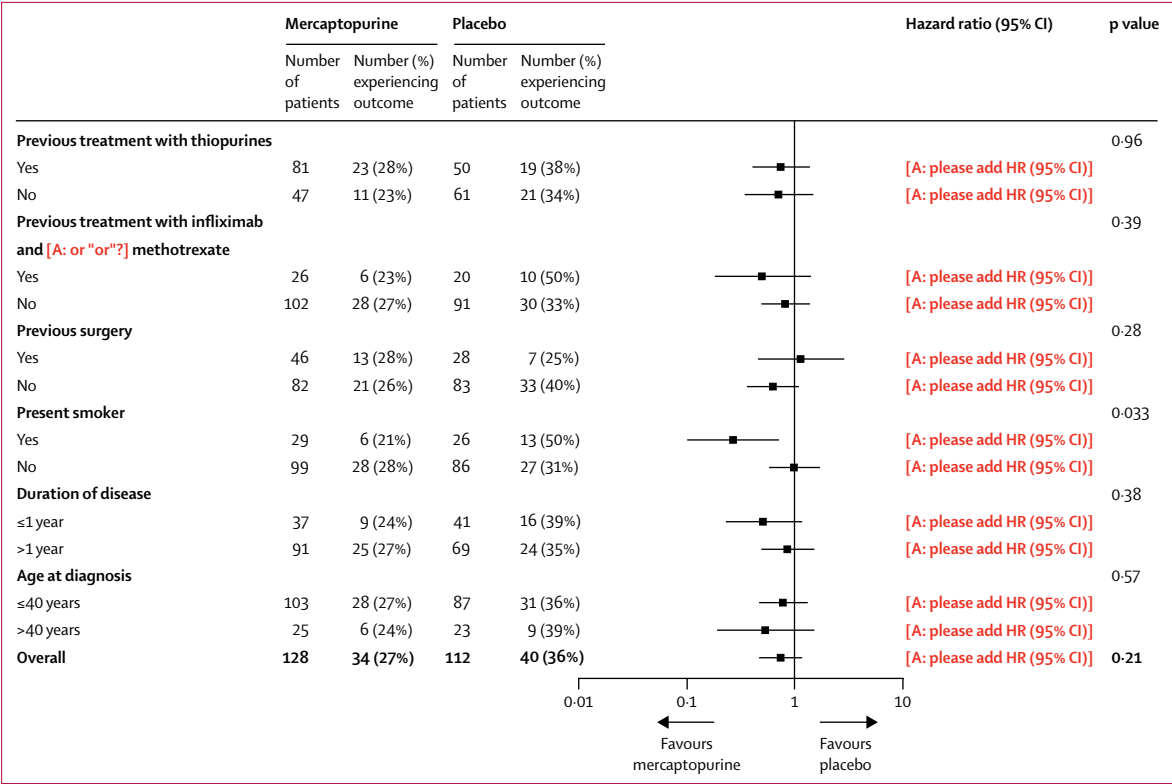


Figure 4: Subgroup analyses of secondary outcome of clinical recurrence [A: are p values p_{interaction}?]

remained in the study at week 157 after randomisation, 128 underwent a colonoscopy, and a Rutgeerts score was available for 124. [A: please provide numbers in each group] Of these, 95 (77%) had some form of endoscopic recurrence (score >i0). [A: please provide numbers in each group] [A: deleted definition of endoscopic recurrence secondary endpoint to avoid repetition] 29 (33%) of xx patients in the mercaptopurine group and 28 (39%) of xx [A: please specify denominators for each group] in the placebo group had endoscopic recurrence with a Rutgeerts score of i2 or greater (adjusted odds ratio 0.66, 95% CI 0.26–1.67; p=0.38). We noted a similar pattern at week 49. [A: Please provide data in the appendix and OR, 95% CI and p value here] Week 157 CDEIS scores did not differ significantly between groups. [A: Please provide data in the appendix and OR, 95% CI and p value here] Similarly, none of the CDEIS subgroup analyses showed a significant interaction with treatment. [A: data not shown? And what about the subgroup analyses for endoscopic recurrence, mentioned in the Methods section?]

Of the 168 patients who had a Rutgeerts score calculated at week 49, faecal calprotectin concentrations were available in 126 patients. [A: how many in each group?] Of the 124 patients who had a Rutgeerts score calculated at week 157, faecal calprotectin concentrations were available in 88 patients (appendix p 12). [A: how many in

30

each group?]

These data were combined to generate ROC curves to examine test accuracy at predicting endoscopic recurrence and remission. In both scenarios, the faecal calprotectin measurement proved to be a poor [A: in what way? Inaccurate?] test, with an area under the curve of 0.7 [A: please provide to 2 dp] (95% CI 0.63–0.77) for recurrence and 0.66 (0.58–0.75) for remission. [A: correct?] Selecting a faecal calprotectin concentration of 50 µg/g (the manufacturer's [A: who? Please specify company and location] cutoff) to predict endoscopic recurrence produced a sensitivity of 84.4% (95% CI 77.0–91.9), specificity of 44.4% (35.6–53.1), positive predictive value of 52.4% (44.3–60.5), and negative predictive value (NPV) of 79.7% (70.2–89.2). Increasing the cutoff concentration to 100 µg/g produced a sensitivity of 72.2% (95% CI 63.0–81.5), specificity of 62.1% (53.6–70.6), positive predictive value of 58.0% (48.9–67.2), and NPV of 75.5% (67.1–83.8). The NPV for the prediction of endoscopic remission with a faecal calprotectin concentration of 50 µg/g was 81.4% (95% CI 75.0–87.7) and with a concentration of 100 µg/g it was 83.9% (77.1–90.7; appendix p 9). Analysis of faecal calprotectin as a time-varying covariate suggested that, for every 100-unit increase in faecal calprotectin, the HR for the primary endpoint (data available for 31 [74%] of 42 patients who reached the primary endpoint) increased by 18% (HR 1.18, 95% CI 1.08–1.28; p=0.0002).

102 (92%) of 111 patients had 6-thioguanine nucleotide concentrations measured at week 49, and 64 (72%) of 89 who remained on mercaptopurine had concentrations measured at week 157. 6-thioguanine nucleotide concentrations were grouped according to the target therapeutic range (235–450 pmol per 8×10⁸ red blood cells [A: correct expansion of RBC?]). At week 49, 61 (60%) of 102 patients had subtherapeutic concentrations, versus 40 (63%) of 64 at week 157 (appendix p 13). [A: was this difference significant? Please provide HR, 95% CI, and p value] In the corresponding time-varying covariate analysis of 6-thioguanine nucleotide concentrations in patients receiving mercaptopurine, the association with the primary outcome was not significant (HR 0·80, 95% CI 0·565 [A: please give to 2 dp]–1·13; p=0·21).

IBDQ data were available for 203 (85%) of 240 randomly assigned patients at week 49 and 155 (65%) at week 157. [A: please provide numbers per group] Overall mean or total IBDQ scores did not differ significantly between groups. [A: please provide data (ie, OR/HR, 95% CI, and p value)] [A: where are these data shown? Could they be included in the appendix?]

The incidence and types of adverse events were similar in the mercaptopurine and placebo groups (table 2 and appendix p 10). Adverse events caused discontinuation of treatment in 80 (33%) of 240 patients: 39 (30%) of 128 in the mercaptopurine group versus 41 (37%) of 112 in the placebo group. Of the 1747 [A: 1745 according to supplementary table 7. Please check] reported adverse events, four (<1%) were malignancies (three in the mercaptopurine group and one in the placebo group: basal cell carcinoma, breast cancer, and two cases of lentigo maligna), [A: which in which group?] and one

patient on placebo died of ischaemic heart disease. 171 (18%) of 947 events in the mercaptopurine group and 184 (23%) of 798 in the placebo group were infections. Mercaptopurine was temporarily stopped in 32 patients on mercaptopurine because of blood test values [A: that showed what?] or other side-effects. Placebo was temporarily discontinued in 35 patients. [A: for what reasons?] [A: deleted repetition of dose reduction details]

14 pregnancies were reported during the course of the trial, with 12 healthy outcomes. [A: successful births?] One spontaneous abortion occurred at about 21 weeks gestation [A: in which group?] and one congenital anomaly (heart murmur, septal defect, and hydrocephalus) occurred in a patient [A: or fetus?] in the placebo group.

In a post-hoc analysis, complete endoscopic remission (Rutgeerts score i0) was maintained in proportionally more patients on mercaptopurine than placebo at both week 49 (30% vs 14%) and week 157 (23% vs 13%; [A: rounding correct?] appendix pp 14–15 [A: any statistical analysis available? Ie, p value]). In a [A: post-hoc?] subgroup analysis, mercaptopurine was more effective at preventing endoscopic recurrence in patients with previous thiopurine exposure (odds ratio 0·25, 95% CI 0·09–0·70) than in thiopurine-naïve patients (3·00, 1·00–9·04; p=0·001) [A: are these data shown in any citeable figure or table? Please add “(data not shown)” if not]. Endoscopic recurrence, defined as Rutgeerts score greater than i0 [A: i0 correct?] (ie, anything other than complete remission), was present in 58 (64%) of 91 patients in the mercaptopurine group versus 62 (82%) of 76 in the placebo group at week 49 (p=0·01), and in 47 (70%) of 67 in the mercaptopurine group versus

	Mercaptopurine (n=128)				Placebo (n=112)			
	Mild	Moderate	Severe	Total	Mild	Moderate	Severe	Total
Cancers	0	2 (2%)	0	2 (2%)	0	0	1 (1%)	1 (1%)
Abnormal liver function test	0	4 (3%)	0	4 (3%)	0	5 (4%)	0	5 (4%)
Gastrointestinal symptoms								
Abdominal pain	15 (12%)	32 (25%)	19 (15%)	66 (52%)	10 (9%)	42 (38%)	15 (13%)	67 (60%)
Constipation or diarrhoea	12 (9%)	19 (15%)	6 (5%)	37 (29%)	7 (6%)	23 (21%)	7 (6%)	37 (33%)
Nausea or vomiting	13 (10%)	24 (19%)	8 (6%)	45 (35%)	12 (11%)	16 (14%)	2 (2%)	30 (27%)
Other	14 (11%)	16 (13%)	4 (3%)	34 (27%)	12 (11%)	16 (14%)	0	28 (25%)
Headache	9 (7%)	17 (13%)	0	26 (20%)	6 (5%)	11 (10%)	3 (3%)	20 (18%)
Infections	31 (24%)	45 (35%)	5 (4%)	81 (63%)	24 (21%)	38 (34%)	6 (5%)	68 (61%)
Joint pain or arthralgia	13 (10%)	23 (18%)	4 (3%)	40 (31%)	8 (7%)	26 (23%)	2 (2%)	36 (32%)
Other [A1]	22 (17%)	55 (43%)	8 (6%)	85 (66%)	18 (16%)	35 (31%)	9 (8%)	62 (55%)
Pain	7 (5%)	8 (6%)	3 (2%)	18 (14%)	4 (4%)	10 (9%)	3 (3%)	17 (15%)
Pancreatitis	0	1 (1%)	0	1 (1%)	0	0	1 (1%)	1 (1%)
Rash	14 (11%)	9 (7%)	1 (1%)	24 (19%)	12 (11%)	2 (2%)	0	14 (13%)
Worsening of Crohn's disease	6 (5%)	13 (10%)	5 (4%)	24 (19%)	3 (3%)	20 (18%)	6 (5%)	29 (26%)

[A: who were adverse events categorised? CTCAE? Which version?] Data are number of patients with one or more adverse event in that category. Patients who had more than one adverse effect in the same category but different severity are counted in the most severe category. [A1: please specify]

Table 2: Adverse events

48 (84%) of 57 in the placebo group at week 157 ($p=0.07$).
 [A: are these data shown in any citeable figure or table?
 Please add "(data not shown)" if not]

Discussion

To our knowledge, this is the largest randomised, double-blind study to assess the efficacy of mercaptopurine in the prevention of postoperative Crohn's disease. The primary outcome, a composite of clinical recurrence of Crohn's disease (Crohn's Disease Activity Index >150 plus 100 point increase in score) and the need for anti-inflammatory rescue treatment or primary surgical intervention, was reached by 13% of patients in the mercaptopurine group versus 23% in the placebo group (adjusted $p=0.07$); however, clinical recurrence was significantly more common in smokers, in whom mercaptopurine proved beneficial, with a NNT of three. The secondary outcome of endoscopic recurrence was recorded in a third of patients in each group, with no significant difference between groups; however, in a post-hoc analysis, mercaptopurine was significantly more effective than placebo at maintaining complete endoscopic remission. Although there was no significant difference in the prespecified primary clinical efficacy endpoint, the subgroup analyses provide relevant insights in terms of clinical prediction of response and outcome, and in terms of the challenges in assessing outcome by endoscopic or clinical criteria.

Findings from this study confirm that smoking affects the clinical course of Crohn's disease, as well as response to treatment. Of the factors assessed, the primary endpoint was only significantly different between smokers and non-smokers, whereas no differences were reported by age, sex, or a history of previous surgery [A: add duration of disease, previous treatments, and thiopurine status here?]. The data highlight the importance of smoking cessation in disease management and support findings from previous studies¹⁵⁻¹⁷ that showed that surgical recurrence increases with the number of cigarettes smoked each day, and that smoking cessation reduces clinical and surgical recurrence. Treatment with mercaptopurine to delay or prevent postoperative recurrence is particularly effective in people who continue to smoke [A: which study are you referring to here?]; thus, in smokers, thiopurine treatment seems to be justified in the early postoperative period. In non-smokers, the data do not provide a sufficiently strong rationale for immediate initiation of treatment in the postoperative period. A considered approach involving colonoscopy in the first 6-12 months is likely to [A: OK? or "might"?] be beneficial in this group.

This study is one of the largest to report on endoscopic recurrence of Crohn's disease, and is important for several reasons. First, the incidence of any endoscopic recurrence was 76% [A: Results state 77%. Which is correct?] at 3 years, which is similar to the 85% reported

previously.¹³ Second, over a 3-year period, there was a poor association between endoscopic and clinical recurrence. [A: correct?] There are several possible explanations for this finding, and there is no consensus as to whether to prioritise clinical outcomes over endoscopic outcomes. Third, mercaptopurine seems to maintain complete endoscopic remission (i0), whereas using a cutoff score of at least i2 to define endoscopic recurrence revealed no difference between treatment and placebo groups. Fourth, our study is, to our knowledge, the largest comprehensive assessment of faecal calprotectin in postoperative Crohn's disease. Using a cutoff of 50 $\mu\text{g/g}$, the NPV for recurrence was 79.7%, which decreased to 75.5% by increasing the cutoff to 100 $\mu\text{g/g}$. The corresponding NPVs for the prediction of endoscopic remission were 81.4% and 83.9%, respectively. If mucosal integrity is the goal, these values might not [A: OK? or "are unlikely to"] provide the confidence to abandon endoscopic assessment. The performance of faecal calprotectin was poorer than reported in the POCER study (NPV of 94%).¹¹ Reported differences between studies are probably due to differences in study methods, since in the POCER study, an endoscopic score of i2 was imputed for all missing values; no imputations were made in our study.

Several important factors should be considered when interpreting these findings. Based on existing data, power calculations estimated a 20% difference between mercaptopurine and placebo groups. Clinical recurrence rates were 23.2% in the placebo group and 12.5% in the treatment group: a difference of 10.7%. These rates are lower than those in studies by Hanauer and colleagues¹⁸ (40% and 75% [A: what are these two percentages for—treatment vs placebo?]) and Ardizzone and colleagues¹⁹ (25%), on which the power calculations were based. This marked difference between recurrence rates is probably a result of differing primary outcome definitions; clinical scoring systems advocated to identify disease relapse in clinical trials such as CDAI have flaws, especially in the postoperative setting.²⁰ We used a composite outcome that was based on a disease activity score (CDAI >150 and a 100-point increase from baseline) and the need for medical treatment. In view of the difficulties of using the CDAI postoperatively, we judged this definition of clinical recurrence to be robust. An analysis of the individual items of the CDAI or the need for rescue treatment was part of the secondary outcomes and performed less effectively than the primary outcome. [A: what do you mean by "performed less effectively"? "was not significant"?] The Rutgeerts score attempts to make the assessment of endoscopic recurrence an objective exercise, but has never been prospectively validated.¹³ We selected a score of at least i2 as a secondary endpoint, in line with previous studies, including the study by Hanauer and colleagues.¹⁸ However, the limitations of this approach are well recognised; there is little difference between i1 (≤ 5 aphthous ulcers) and i2

(>5 aphthous ulcers or larger lesions confined to the anastomosis), and inter-observer variation is an issue. In a substudy²¹ of the TOPPIC trial, inter-observer agreement on 43 endoscopic images was measured by five investigators; complete agreement occurred in only 79% of cases. Although centralised reading could overcome some of the inter-observer variation in endoscopic scoring in future studies, an alternative approach might be to regard complete mucosal healing as the preferred therapeutic target in Crohn's disease, and to identify maintenance of endoscopic remission (i0) as the target in postoperative Crohn's disease. A review of the scoring of endoscopic recurrence is warranted.

Optimum dosing in all patients was also difficult to achieve in the context of a double-blind study and a protocol-led dose adjustment strategy. Of the 240 patients, 104 (43%) received treatment at the initial dose for the duration of the study. Data available at the end of the study show that about 60% of patients randomly assigned to mercaptopurine were on subtherapeutic doses, and a stronger treatment effect might have been noted had 6-thioguanine nucleotide results been available to optimise the dose during the study. The rates of discontinuation of treatment and withdrawal or loss to follow-up in this study are similar to those in previous work. For example, Ardizzone and colleagues¹⁹ reported treatment discontinuations owing to adverse events in 15 (11%) of **xx** patients in the azathioprine group versus six (4%) of **xx** in the mesalazine group, [A: please provide numbers] although data on treatment discontinuation within other trials are less transparent. [A: please clarify what you mean by "less transparent", than what?] Analysis of these data was on an intention-to-treat basis and therefore the effect of the drug taken at full dose in an individual patient is likely to have been underestimated. In clinical practice, many patients taking thiopurines are likely to be [A: OK? or simply "are"?] under-dosed initially, but are identified on the basis of mean corpuscular volumes or, more recently, available metabolite testing.²²

Adverse events were noted frequently in both groups but were generally mild. Rates of pancreatitis and malignancy were lower than expected. Unusually for a clinical trial, we did not remove patients who became pregnant during the trial, in-keeping with accepted clinical practice. We noted 14 pregnancies, with 12 healthy outcomes. No fetal malformations occurred in the mercaptopurine-treated group. Masked safety monitoring contributed to the validity of the results.

The strengths of this study include the double-blind design, the association [A: comparison?] of symptom scores with endoscopic findings, the assessment of faecal calprotectin in a large number of patients in the postoperative setting, and a demonstration of the potential usefulness of 6-thioguanine nucleotide concentrations in patient management. The study also

included patients from 29 UK centres, both secondary and tertiary hospitals, which makes it generalisable [A: to the UK population?]. Limitations include the absence of therapeutic drug monitoring with dose adjustment, missing colonoscopy data in 20% of eligible patients, and the absence of centralised endoscopy reading. Furthermore, we included CDAI measurement within the primary outcome even though it has been previously criticised in this setting. The 36-item Short Form quality of life instrument underwent internal text changes at the time of trial start-up. The reporting of these results was deemed not to be compliant with 36-item Short Form licensing terms and these results are therefore not presented.

A definitive study of postoperative prevention of Crohn's disease has proved difficult to undertake. [A: edits OK?] The PREVENT study²³ was terminated early because of small numbers of patients reaching the primary outcome. The PREVENT study²³ had selective inclusion criteria, and no difference was reported in clinical relapse between those on infliximab and those on placebo at week 76, although an endoscopic effect was noted. A smaller study²⁴ that compared early azathioprine initiation with azathioprine driven by endoscopic findings at week 26 was stopped after 6 years because of slow recruitment, with no meaningful conclusions [A: meaning the study was underpowered to draw any conclusion?]. Although our study was underpowered to detect the reported treatment effect, and many patients were under-dosed with mercaptopurine, our data nonetheless provide some evidence of efficacy of mercaptopurine in the context of postoperative prevention. Indeed, a meta-analysis of these data with the two other randomised placebo-controlled trials of thiopurines in the postoperative setting^{15,18} shows a significant reduction in postoperative clinical relapse at 12 months (relative risk 0.57, 95% CI 0.38–0.85; appendix p 11). [A: 0.58, 0.41–0.82 according to appendix p 11. Which is correct?] Taken with the other recent data, our study helps to make progress towards a treatment algorithm for all patients after surgery for Crohn's disease, with smoking habit the key determinant affecting management.

Several areas now require further clinical studies, [A: edits OK?] including putative mechanisms for the effect of smoking on Crohn's disease,²⁵ and smoking intervention studies. The efficacy and safety of mercaptopurine compared with anti-tumour-necrosis-factor (TNF) as postoperative preventative treatment is a key issue to investigate. At present, anti-TNF treatment is reserved for patients who are intolerant or unresponsive to thiopurine, but the safety, efficacy, and cost of these drugs is under continuous reassessment. Endoscopic findings and faecal calprotectin remain important components of disease assessment, but the exact parameters that best define postoperative recurrent disease remain to be elucidated.

Contributors

CM [A: CMO r CMu?], IA, AC, JM, MGD, MC, AM, DB, [A: who is DB? I can't find anyone with these initials in the authorship] RJP, NAK, and JS conceived, designed, and formulated the statistical analysis of the study. CM, [A: CMO r CMu?] IA, HE, CK, SL, [A: SLa or SLe?] NAK, and JS prepared the first draft of the paper. All other authors contributed to data acquisition, reviewed the paper, and approved the submitted version.

Declaration of interests

We declare no competing interests.

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[A: references renumbered. Please check citations are correct]

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